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Long-term Visual and Ocular Sequelae in Patients with Congenital Cytomegalovirus Infection

Haoxing Jin, MD[1], **Gail J. Demmler-Harrison, MD**[2,4], **David K. Coats, MD**[2,3], **Evelyn A. Paysse, MD**[2,3], **Amit Bhatt, MD**[2,3], **Jane C. Edmond, MD**[2,3], **Kimberly G. Yen, MD**[2,3], **Paul Steinkuller, MD**[2,3], and **Jerry Miller, MS, PhD**[2] **for The Congenital CMV Longitudinal Study Group**[2,4]

[1]School of Medicine, Baylor College of Medicine, Houston, TX

[2]Texas Children's Hospital, Houston, TX

[3]Department of Pediatric Ophthalmology, Baylor College of Medicine, Houston, TX

[4]Department of Pediatrics, section of Infectious Disease, Baylor College of Medicine, Houston, TX

Abstract

Background—Cytomegalovirus (CMV) is the most common congenital viral infection in the United States. Visual and ocular sequelae in adolescents and adults who are congenitally infected with CMV have not been well studied. Better understanding of the long-term visual and ocular sequelae can help with early detection, intervention, and appropriate educational accommodations.

Methods—This study evaluated 237 (77 symptomatic, 109 asymptomatic, and 51 control) patients who underwent a series of age-appropriate ophthalmologic, audiologic, and neurodevelopmental examinations from 1982 to 2013. The frequency and etiology of visual impairment and other non-ophthalmologic findings were recorded for each patient. Ophthalmologic findings were tabulated and risk factors for abnormalities were analyzed.

Results—Fourteen of the 77 (18.2%) symptomatic and none of the asymptomatic and control subjects had severe visual impairments ($p \leq 0.006$). Moderate visual impairment did not differ between symptomatic and asymptomatic subjects. Three asymptomatic subjects had retinal scars. The most common visual or ocular sequelae in the symptomatic group were strabismus (23.4%), chorioretinal scars (19.5%), cortical visual impairment (14.3%), nystagmus (14.3%), and optic nerve atrophy (11.7%). Three symptomatic patients had delayed visual deterioration due to later occurring retinal disorders: peripheral retinal scar, rhegmatogenous retinal detachment, and Coats' disease.

Conclusion—Symptomatic CMV patients experienced more ophthalmologic sequelae and significantly worse visual outcomes than asymptomatic CMV and control patients. Later occurring retinal disorders were found in symptomatic patients, and there is no clear evidence that CMV can reactivate in the retinas of children who were congenitally infected. Major risk factors for severe

Correspondence: Haoxing (Douglas) Jin, B.S., Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, hjin@bcm.edu, Tel: (832) 459-4403, Fax: (832) 825-4347.

visual impairment included symptomatic status, optic nerve atrophy, chorioretinitis, cortical visual impairment, and sensorineural hearing loss.

Keywords

Long-term; Congenital Cytomegalovirus; CMV; Visual; Sequelae

Introduction

Cytomegalovirus (CMV) is the most common congenital viral infection in the United States, affecting approximately 1% of all live births (30,000–40,000) annually.[1] Eighty to 85% of congenitally infected patients do not readily exhibit clinical symptoms of CMV infection at birth.[1] The remaining 15–20% of the congenitally infected patients, described as having symptomatic congenital CMV infection, often show one or more clinically observable abnormalities, which include microcephaly, jaundice, hepatosplenomegaly, petechiae, hearing loss, and chorioretinitis.[1] The most commonly appreciated and most commonly studied long-term sequelae of congenital CMV infection is progressive sensorineural hearing loss. Neurodevelopmental disabilities are also well documented. The most commonly-reported visual and ocular sequelae in congenital CMV infection are chorioretinitis, optic atrophy, strabismus, and cortical visual impairment.[1–7] However, the long-term visual and ocular outcomes of congenital CMV infection are not as well studied or as well known.

Determining the prevalence and onset of visual and ocular sequelae in patients congenitally infected with CMV is extremely important because early detection can lead to early intervention and appropriate educational accommodations. Long-term, comprehensive prospective studies in patients who are congenitally infected with CMV are lacking within the past two decades. Prior publication on ophthalmologic findings in patients with congenital CMV infection were published more than a decade ago.[3,6,8] The latest publication on congenital CMV outcomes in Sweden and United Kingdom was published in 2013 focused on the hearing and neurodevelopmental aspects on the disease, and reported one case of optic atrophy.[9] The purpose of this study was to update our previous findings,[3] to determine the frequency and type of visual and ocular abnormalities through childhood, adolescence and into early adulthood, and to report associated non-ophthalmologic CMV sequelae as potential risk factors for visual and ocular sequelae in a study population that has been followed for more than 30 years.

Materials and Methods

The study population comprised 237 infants and children who enrolled in a long-term, prospective congenital CMV study (The Houston Congenital CMV Longitudinal Study) since 1982. During 1982–1992, 32,543 newborns delivered at Women's Hospital of Texas (a private hospital that served a primarily white, middle to upper socioeconomic population), Houston TX, were screened for congenital CMV infection via urine culture collected within 3 days of life, as described previously.[10] Of the asymptomatic subjects, 92 were from the screened population and 17 were referred from other sources. Four of the symptomatic cases were from the screened population and 73 were referred from other sources. Of the controls,

44 were from the screened population, and 7 were referred. Earlier visual and ocular exam findings were first described by Coats, et al.[3] Congenital CMV infection diagnosis required isolation in cell viral culture of CMV from the urine of the infant within the first 3 weeks of life as described previously.[3] Symptomatic congenital CMV infection was defined as the presence of one or more of the clinical symptoms associated with CMV infection at birth, after exclusion of other causes of congenital infection. The clinical symptoms associated with symptomatic congenital CMV infection classification at birth were low birth-weight adjusted for gestational age (small for gestational age (SGA)), generalized petechial rash, hepatomegaly, splenomegaly, jaundice at birth, microcephaly (< Lubcenko 10th percentile), seizures, and thrombocytopenia.[1,4] Asymptomatic congenital CMV infection was defined as positive CMV urine cell viral cultures but with no readily observable clinical manifestation of disease at birth, and control subject patients were defined by a normal newborn exam and a negative urine cell viral CMV culture in the first three weeks of life. All controls were CMV-negative at birth, and were selected among screened newborns or referred into the study.

Patients underwent serial age-appropriate, multidisciplinary evaluations, consisting of ophthalmologic examinations by pediatric ophthalmologists, neurodevelopment evaluations, audiologic screening, and urine and salivary CMV viral cell cultures. Ophthalmologic examinations were scheduled at 4–6 weeks, 9–12 months, 18–24 months, 3–3.5 years, 4.5–5 years, 3rd – 4th grade, 7th–8th grade, junior or senior year of high school, and at college graduation age.

From 1982 to 1994 only symptomatic CMV patients received ophthalmologic exams, but beginning in 1995, asymptomatic CMV and control patients were also included because of reports of late onset or reactivation of chorioretinitis in children with asymptomatic congenital CMV infection.[12] Ophthalmologic examination included measurement of best corrected visual acuity, pupils, ocular adnexa, anterior segment, posterior segment, visual fields, extraocular motility and alignment, tonometry, and dilated funduscopic examination with cycloplegic refraction.

Vision was classified as normal, moderate impairment, and severe impairment.[13] Normal vision was defined as best corrected acuity better than or equal to 20/40 on optotype visual acuity testing in each eye for those patients who were able to cooperate, or fix and following on a near object for nonverbal and pre-verbal children. The best-corrected vision required to obtain a driver’s license is 20/40. Moderate visual impairment was defined as best corrected visual acuity better than or equal to 20/200 and worse than 20/40, or the presence of fixation on a near object but no following. Legal blindness is defined as best-corrected vision less than 20/200. Severe impairment was defined as vision worse than 20/200, no demonstrable fix and follow behavior, or no reaction to light. Progression of chorioretinal lesions was used to describe an ongoing lesion that was worsening or expanding, while reactivation referred to the activation of a previously quiescent or healing lesion. Chorioretinitis was defined as acute and active retinal lesion seen by the pediatric ophthalmologist, whereas chorioretinal scars were inactive form of the chorioretinal lesions.

Statistical analysis was done using SPSS software (IBM Corp. Released 1989 & 2015. IBM SPSS Statistics for Windows, Version 23. Armonk, NY: IBM Corp.). Continuous variables were compared between subject groups with t-tests and statistical significance assessed by Pearson Chi-square or Fisher's Exact Test. Kaplan-Meier analysis was used to graph the development of non-normal visual acuity for all subjects. Categorical variables were compared using Chi-square tests for differences in proportions. All p-values were two-sided.

This study was conducted with approval of the Baylor College of Medicine Institutional Review Board for Research on Human Subjects.

Results

The demographic data of the longitudinal CMV study patients, estimated gestational age, birth weight, age at the most recent eye exams, and the average number of eye exams were tabulated in Table 1. The majority of study patients were white. There was no significant difference in race among the three CMV disease status groups. There were significantly more males in the control group compared to symptomatic group ($p = 0.027$). The average age at the most recent eye exam was significantly younger in symptomatic group ($p < 0.001$), which also received a significantly higher number of eye exams ($p < 0.001$). Symptomatic CMV patients had lower estimated gestational age and birth weight than did asymptomatic and control patients ($p \leq 0.002$).

Severe visual impairment was found in 10 (13.0%) symptomatic patients, and was caused by optic nerve atrophy (6/10), chorioretinitis (6/10), cortical visual impairment (7/10), and chronic retinal detachment (1/10) (Table 2). All abnormalities leading to severe visual impairment were diagnosed before the age of 18 in both the symptomatic and asymptomatic groups (Figure 1). Two patients' chorioretinal lesions had progressed during follow up shortly after birth. One had an increase in the number of chorioretinal lesions from one to four within the first month of life with an advancement in the borders of the first lesion. This patient's lesions became stable after the neonatal period. The second patient experienced advancement in size of the two chorioretinal lesions during follow up in the second, fifth, and 24 months of life; which became stable thereafter.

Optic nerve atrophy was a significant cause of severe visual impairment in the symptomatic group, as it was noted in 8 (10.4%) symptomatic, 0 asymptomatic, and 1 (2%) control patients. Optic nerve atrophy was first diagnosed at the average age of 5.4 years for symptomatic patients and at the age of 8.8 years in the control patient. The one control patient had optic nerve atrophy secondary to Leber hereditary optic neuropathy, an unrelated condition. Chorioretinal scars, which usually follow active chorioretinitis, were seen more frequently in symptomatic CMV patients than in asymptomatic CMV and control patients (Table 2). Later occurring retinal disorders (peripheral retinal scar, rhegmatogenous (trauma-induced) retinal detachment, and Coats' disease) were detected in three symptomatic patients. The peripheral retinal scar could be a new onset lesion, but was most likely existing scar that was missed on previous exams due to poor cooperation. The rhegmatogenous retinal detachment was likely trauma related, and the Coats' disease was diagnosed based on vascular changes consistent with the disorder after examination by a retinal specialist. While

chorioretinal scars were unilateral or bilateral in the symptomatic group, only unilateral scars were seen in asymptomatic and control groups (Table 2). One control patient had a 1/8 disc-diameter stable peripheral chorioretinal pigmented scar with normal visual acuity. Cortical visual impairment (CVI) was noted in 11 (14.3%) symptomatic patients at the average age of 5.1 years, and in none of the asymptomatic patients or controls (Table 3). Two of the 11 CVI patients received and were noted to have abnormal visual evoked potentials.

Strabismus was more common (23.4%) in the symptomatic than in asymptomatic (1.8%) or control (3.9%) groups (Table 3), and they were detected at the average ages of 4.5, 10.9, and 15.8 years, respectively. Of the symptomatic patients with strabismus, exotropia was five times more common than esotropia. Nystagmus was detected at the average age of 7.9 years and was only found in symptomatic patients, and it was highly correlated with cortical visual impairment ($p < 0.001$) and severe visual impairment ($p < 0.008$). There were no statistically significant differences among the three disease status groups in mean cycloplegic refraction, prevalence of amblyopia, and anterior segment findings (Table 3). The five cases of anterior segment findings noted in the symptomatic group were corneal stromal scar, anterior polar cataract, microcornea, superficial punctate keratitis, and iris heterochromia. The three anterior segment findings in the asymptomatic group were iris heterochromia, anterior stromal scar, and limbal pannus. The anterior segments findings in the two control patients were Mittendorf's dot, which is a normal embryonic remnant, and superficial stromal opacities, which is a benign finding. Five patients (6.5%) had abnormal optic nerve cupping (cup-to-disc ratio > 0.5) in the symptomatic group versus only one (0.9%) in the asymptomatic ($p = 0.083$) and none in the control groups ($p = 0.156$). There was a slightly, but statistically significant higher prevalence of astigmatism in the symptomatic group compared to the asymptomatic group ($p = 0.049$).

Non-ocular findings, including sensorineural hearing loss (SNHL), microcephaly, abnormal brain CT imaging, and intracranial calcifications were significantly higher in the symptomatic CMV group than in the asymptomatic CMV group (Table 4). SNHL in particular was highly associated with the six leading ophthalmologic findings: optic nerve atrophy, nystagmus, cortical visual impairment, retinal scars, strabismus, and severe visual impairment.

Discussion

Ophthalmologic manifestations of congenital CMV infection can be classified according to the affected anatomical regions – anterior segment, posterior segment, and cortical visual pathways. There was a similar prevalence and severity of anterior segment findings among the three groups, suggesting CMV may have played a limited role in damaging non-neuron-associated cell lines.[12] Anterior segment findings in our subjects, such as corneal stromal scar, anterior polar cataract, microcornea, superficial punctate keratitis, and iris heterochromia were therefore unlikely to be caused by congenital CMV infection, and also were not associated with significant visual impairment.[12] In contrast, the posterior segment of the eye was affected most severely by congenital CMV infection, resulting in optic nerve atrophy and chorioretinal scars, and subsequent severe decrease in visual acuity. In addition,

posterior visual pathways were also severely affected by CMV, causing cortical visual blindness.[3,11,14,15,17] While the exact pathogenesis of CMV causing visual impairment is unknown, clinical evidence reveals high tropism of CMV to nerve cells.[17] In addition, since symptoms at birth are associated with an earlier maternal infection during pregnancy,[18, 19] we highly suspect that the virus's high tropism to rapidly developing neurons during the first trimester of pregnancy is responsible for the neuron-related damages as seen in retina scar, optic nerve atrophy, cortical visual impairment, microcephaly, and sensorineural hearing loss. The high prevalence of strabismus in symptomatic patients most likely developed from optic nerve atrophy and chorioretinal scars. Nystagmus likely occurred from CMV's direct involvement in the central nervous system, or was associated with early onset bilateral moderate to severe vision impairment. Although four cases (3.7%) of chorioretinal scars were seen in the asymptomatic group, the lesions were in the periphery and did not cause noticeable visual impairment.

The presence of clinical symptoms of CMV infection at birth, and especially that of microcephaly, was the most important predictor for developing severe visual impairment in patients congenitally infected with CMV.[16] In addition, SNHL was also associated with decreased visual acuity ($p = 0.028$) in symptomatic patients. The combination of these two sensory disorders would potentially make communication with these patients a challenge.

Progressive hearing loss is common in symptomatic congenital CMV. However, there have been limited reports on late onset, progressive, or reactivation of CMV chorioretinitis in congenital CMV in otherwise normal and immunocompetent individuals,[2, 11, 20] which is probably due to the rarity of the event and the limited follow up time in most studies. The three patients who were noted to have later occurring retinal disorders were all symptomatic at birth who developed other visual and ocular and developmental sequelae. Although the possibility of late onset or reactivation of CMV chorioretinitis cannot be excluded, two cases had plausible alternative diagnoses (trauma and Coats' Disease), and the one case of later detected retinal scar was located in the far periphery, and was likely missed on previous exams. It has been thought that chorioretinal lesions caused by congenital CMV infection rarely progress postnatally,[21] and there is no clear evidence from the present study that CMV in the retina can reactivate in congenitally infected patients.

Symptomatic patients who do not experience retinal or posterior visual pathway lesions early in life should expect to have similar visual acuity to that of individuals with asymptomatic congenital CMV and uninfected controls.

Unlike SNHL, which can be late-onset and is commonly progressive in asymptomatic congenital CMV infection,[22,23,24–27] the chorioretinitis associated with asymptomatic congenital CMV infection did not progress and visual performance was comparable to that of normal healthy controls into young adulthood.[21]

One limitation of our study was ophthalmologic examination in younger patients was difficult, which made examining the peripheral retina challenging at times. In addition, our study sample came from a private maternity hospital, which served at the time a primarily white, middle to upper class, and educated socioeconomic population of the community.

Future studies with more diverse sample population may make the clinical findings more generalizable.

In summary, strabismus, optic atrophy, cortical visual impairment, and chorioretinitis were the most common long-term visual and ocular findings causing moderate to severe visual impairment in subjects with symptomatic CMV status at birth. Progressive chorioretinitis was rare and only occurred in two patients and was limited to early in life. Later-detected retinal disorders were seen in the present study in symptomatic CMV patients; however, since these late onset retinal lesions had plausible alternative diagnoses by specialists, there was no clear evidence that congenital CMV infection can lead to late onset or reactivation of chorioretinitis.

Given our findings, we recommend yearly ophthalmologic examination in patients with symptomatic congenital CMV infection who have ocular or visual disorders detected in infancy. Asymptomatic patients, newborns who fail their newborn hearing screen, and those who were identified to be congenitally infected with CMV via a congenital CMV screening program should also receive a baseline ophthalmologic examination. An abnormal baseline ophthalmologic examination warrants annual follow up whereas if the exam is normal, they can be followed as clinically indicated by signs and symptoms of visual problems.

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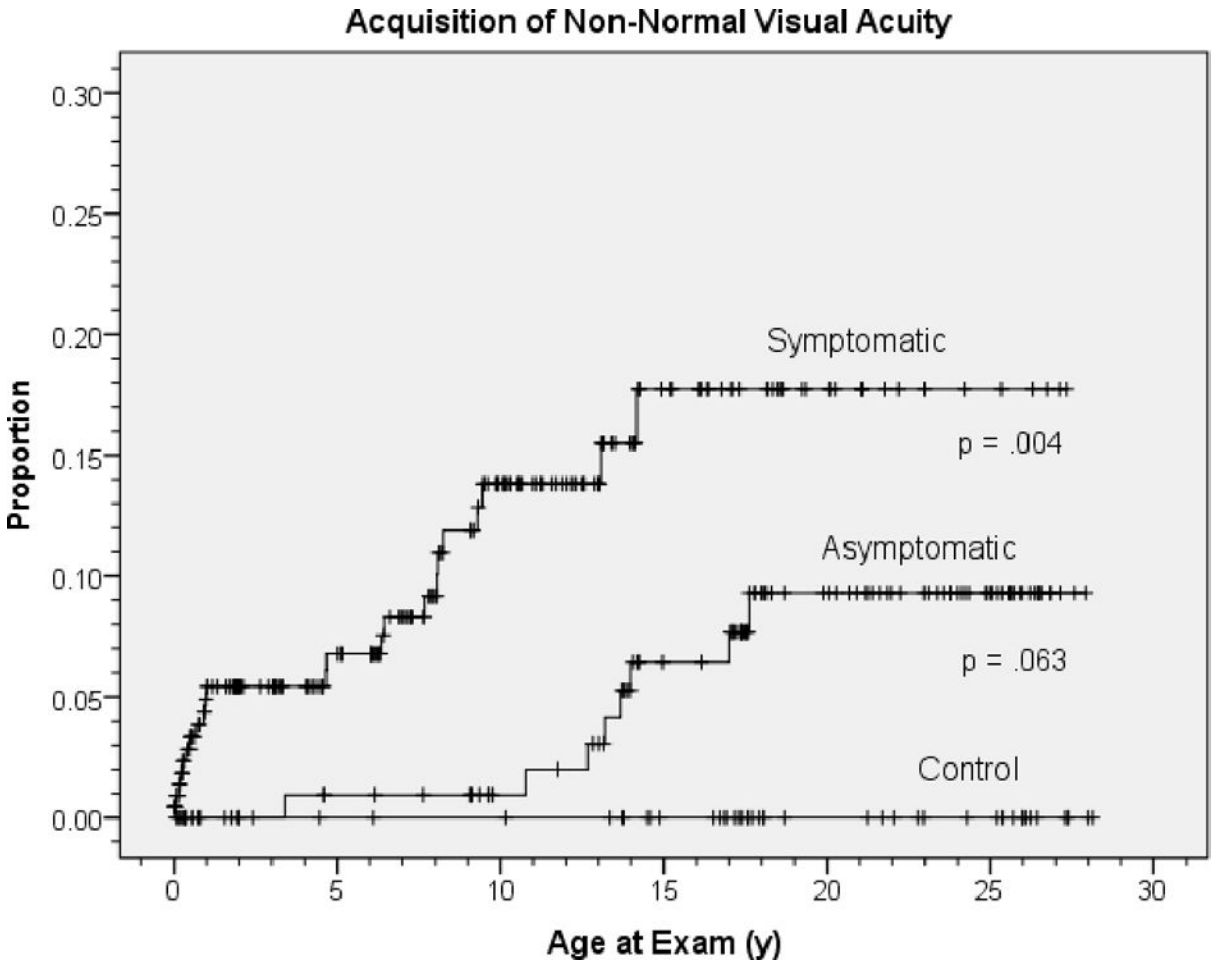

Figure 1.

Kaplan Meier analysis showing age of last acquisition of abnormal visual acuity as measured by the best-corrected vision.

Table 1

Demographic data of newborns (N=237) with asymptomatic and symptomatic congenital cytomegalovirus (CMV) and controls

				Significance (p-values)[Δ]:		
	Symptomatic	**Asymptomatic**	**Control**	**S-A**	**S-C**	**A-C**
No of patients	77	109	51			
M/F	36/41	60/49	35/16	0.265	0.027	0.164
White	63 (81.8%)	94 (86.2%)	46 (91.2%)	0.413	0.192	0.481
Hispanic	19 (24.7%)	10 (9.2%)	2 (3.9%)	0.004	0.002	0.341
Non-Hispanic	44 (57.1%)	84 (77.1%)	44 (86.3%)			
African American	12 (15.6%)	15 (13.8%)	5 (9.8%)	0.728	0.345	0.481
Asian	2 (2.6%)	0 (0%)	0 (0%)	0.17	0.517	n/a
EGA[*](wks)	37.4, sd=2.2, (range 32–41.5)	38.44, sd=2.04, (range 32–41.9)	39.8, sd=1.8, (range 32–42)	0.002	< .001	< .001
Birth weight[*](kg)	2.38 (1.09–4.22)	3.23(1.43–4.98)	3.39 (1.75–4.17)	<.001	<.001	0.089
Age at first retinal scar detection	4.9 (median=1.0), sd=7.1	6.2 (median=5.8), sd=5.7	12.8	0.472	–	–
Mean age at most recent eye exam[*](yr)	12.0 (median = 11.7) (1wk–27.3y)	17.1 (median = 17.6) (<1mo–27.9y)	16.9 (median = 17.6) (2mo–28.1y)	<.001	0.001	0.93
Average # eye exams[*]	7.52 (1–21)	3.94 (1–8)	2.63 (1–7)	<.001	<.001	<.001

EGA = Estimated gestational age.

[*]Values in parentheses are ranges.

[Δ]Symptomatic and Asymptomatic (SA); Symptomatic and Controls (S-C); Asymptomatic and Controls (A-C).

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Table 2

Visual impairment and fundus abnormalities in subjects (N=237) with asymptomatic and symptomatic congenital cytomegalovirus (CMV) and controls

				Significance (p-values)[Δ]:		
	Symptomatic	**Asymptomatic**	**Control**	**S-A**	**S-C**	**A-C**
No. of patients	77	109	51			
Vision (at most recent exam)						
Normal	52 (67.5%)	90 (82.6%)	44 (86.3%)	0.017	.017	0.554
Moderate impairment	5 (6.5%)	5 (4.6%)[*]	0 (0%)	0.743	0.156	0.178
Severe impairment	10 (13.0%)	0 (0%)	0 (0%)	< .001	0.006	n/a
Not evaluated	10 (13.0%)	14 (12.8%)	7 (13.7%)	0.977	0.904	0.878
Optic atrophy	8 (10.4%)	0 (0%)	1 (2.0%)	.001	0.085	0.319
Unilateral	3 (3.9%)	0 (0%)	0 (0%)			
Bilateral	5 (6.5%)	0 (0%)	1 (2.0%)[†]			
Retinal Lesions[**]	20 (26.0%)	4 (3.7%)	1 (2.0%)	< .001	< .001	1.000
Unilateral	11 (55%)	3 (75%)	1 (100%)[‡]	.273	1.000	n/a
Bilateral	8 (40%)	0 (0%)	0 (0%)			
Not Noted	1 (5%)	1 (25%)	0 (0%)			
Retinal Detachment	1 (1.3%)	0 (0%)	0 (0%)	0.170	0.517	n/a

[*] Four of these 5 patients' visual acuities were taken without correction, one had glaucoma

[**] Retinal lesions include acute chorioretinitis, retinal scars, and all non-CMV-related lesions

[†] Leber's hereditary optic atrophy.

[‡] Congenital hypertrophy of retinal pigmented epithelium.

[Δ] Symptomatic and Asymptomatic (S-A); Symptomatic and Controls (S-C); Asymptomatic and Controls (A-C).

Table 3

CVI, strabismus, and other non-fundus findings in subjects (N=237) with asymptomatic and symptomatic congenital cytomegalovirus (CMV) and controls

				Significance (p-values)[Δ]:		
	Symptomatic	**Asymptomatic**	**Control**	**S-A**	**S-C**	**A-C**
No. of patients	77	109	51			
Cortical visual impairment	11 (14.3%)	0 (0%)	0 (0%)	<.001	0.003	n/a
Strabismus	18 (23.4%)[*]	2 (1.8%)	2 (3.9%)	<.001	0.003	0.593
Esotropia	3 (3.9%)	0 (0.0%)	2 (3.9%)	1.000	0.053	0.333
Exotropia	15 (19.5%)	2 (1.8%)	0 (0.0%)			
Amblyopia	3 (3.9%)	3 (2.8%)	2 (3.9%)	0.693	1.000	1.000
Anterior segment findings	5 (6.5%)	3 (2.8%)	2 (3.9%)	0.279	0.313	0.654
Nystagmus	11 (14.3%)	0 (0%)	0 (0%)	<.001	<.001	n/a
Mean cycloplegic refraction[†]						
OD	−1.11	−1.1	−0.96	0.983	0.821	0.765
OS	−1.03	−1.19	−0.83	0.762	0.772	0.436
Astigmatism	22 (28.6%)	18 (16.5%)	9 (17.6%)	0.049	0.158	0.858
Cupping	5 (6.5%)	1 (0.9%)	0 (0%)	0.083	0.156	1.000

[*] One symptomatic patient's strabismus was unclassified.

[†] Spheroequivalent.

[Δ] Symptomatic and Asymptomatic (S-A);

Symptomatic and Controls (S-C);

Asymptomatic and Controls (A-C).

Table 4

Nonophthalmologic sequelae and comorbidities in subjects (N=237) with asymptomatic and symptomatic congenital cytomegalovirus (CMV) and controls

				Significance (p-values)[Δ]:		
	Symptomatic	**Asymptomatic**	**Control**	**S-A**	**S-C**	**A-C**
Microcephaly (< Lubcenko 10th percentile)	34 (44.2)	11 (10.1%)	0 (0%)	< .001	< .0.001	0.063
CT Scan	75 (97.4%)	100 (91.7%)	2 (4%)	0.127	< .001	< .001
[*] Abnormal brain CT	63 (81.8%)	49 (45%)	unknown	< .001	n/a	n/a
Not abnormal brain CT	12 (15.6%)	51 (46.8%)	unknown			
Neurodevelopmental delay	24 (31.2%)	4 (3.7%)	1 (2.0%)	< .001	< .001	1.000
Sensorineural Hearing Loss	53 (68.8%)	19 (17.4%)	1 (2.0%)	< .001	< .001	0.006
Unilateral	9 (11.7%)	11 (10.1%)	0 (0%)	0.001	1.000	0.450
Bilateral	44 (57.1%)	8 (7.3%)	1 (2.0%)			

[Δ] Symptomatic and Asymptomatic (S-A); Symptomatic and Controls (S-C); Asymptomatic and Controls (A-C).

[*] Abnormal brain CT include periventricular calcification, periventricular leukoplakia, cerebral atrophy, cortical migratory abnormalities, ventriculomegaly, and microcephaly.

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